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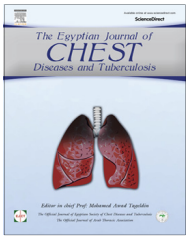

ORIGINAL ARTICLE

Effect of comorbidities on response to pulmonary rehabilitation in patients with chronic obstructive pulmonary disease

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KEYWORDS

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Abstract *Background and objective:* Patients with chronic obstructive pulmonary disease (COPD) typically manifest with worsening dyspnea, poor exercise tolerance and diminished quality of life. In addition, comorbidities are commonly reported in these patients, complicating management strategies. Pulmonary rehabilitation (PR) is an evidence-based multimodality therapy increasingly prescribed for symptomatic COPD patients. This study aimed to assess the impact of comorbidities on achieving proper response to PR in patients with COPD.

Methods: Forty patients with COPD were enrolled in PR program of upper and lower extremity exercise, and were prospectively followed. The minimal clinically important difference (MCID) was used as a cut-off to determine response in six-minute walk distance (6MWD), modified Medical Research Council (mMRC) dyspnea scale, Saint George Respiratory Questionnaire (SGRQ) and estimated maximum oxygen consumption (VO_{2max}). According to comorbidities patients were divided into three groups: patients without comorbidities, patients with one comorbidity and patients with more than one comorbidity.

Results: Comorbidities were diagnosed in 34 patients (85%). Patients with one or more comorbidity had significantly worse baseline mMRC, 6MWD, SGRQ score and VO_{2max} but not FEV_1%. Thirty-two patients (80%) showed improvements beyond the MCID. Factors that predicted better response included higher arterial $PaCO_2$, presence of osteoporosis, and lower baseline 6MWD, mMRC and VO_{2max}.

Conclusions: Pulmonary rehabilitation can be offered to COPD patients from different severity stages. Comorbidities occur very commonly in patients with COPD and their presence worsens the

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baseline functional status in these patients which makes them more liable to achieve larger benefits from PR.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent diseases in the world [1]. It afflicts around 1% of the global population and its prevalence rises steeply after the age of 40 [2]. The hallmark of COPD is progressive airflow limitation secondary to noxious stimuli, the most important of which is tobacco smoke. This is manifested as progressively worsening dyspnea and poor exercise tolerance [3].

Pathologically, COPD involves chronic inflammation of the lung, particularly in peripheral airways and parenchyma and this inflammation increases during acute exacerbations [4]. Inflammation is not only a pulmonary problem in COPD, but it has been demonstrated that systemic inflammation is a constant feature in the disease [5]. This diffuse inflammatory state is thought to be due to spill over from the lungs and is responsible for the systemic manifestations of COPD. Systemic inflammation is arguably a contributory factor in the development of several of the comorbidities of COPD or at least leads to its worsening [5].

Pulmonary rehabilitation (PR) is a cornerstone of management of COPD that aims to improve physical well-being while enhancing disease management. In addition to exercise training of lower and upper extremities, the core component of PR, it also incorporates patient education and behavioral change [6]. It is recognized that there is some heterogeneity in response to PR between individuals, with some people not achieving meaningful improvement [7]. Some researchers have striven to gauge the effect of comorbidities on response to PR [8–11]. While some of them noted a negative effect with some comorbidities, [9,11] others have not reported such findings [8,10].

This study aimed to evaluate the impact of baseline functional status as well as common comorbidities on the effect of PR on COPD patients.

Methods

Patients

Patients with COPD who presented to the outpatient clinic with acute exacerbation were offered PR after stabilization of the condition. Comorbidities were observed at the baseline as well as the physiologic and functional status of the patients. Patients were prospectively followed for response to PR according to previously set criteria. Diagnosis of COPD was confirmed by post bronchodilator spirometry and classification was based on the most recent guidelines of the global strategy for chronic obstructive pulmonary disease (GOLD) [3]. Patients with uncompensated respiratory acidosis, history of previous lung surgery, acute heart failure, disabling neuromuscular conditions, ischemic heart disease and cognitive impairment were excluded from the study.

Comorbidities were recorded based on the patients direct questioning, patients' medication list and specific diagnostic tests for certain comorbidities. According to the presence or absence of comorbidities as well as its frequency, patients were divided into three groups. The first group was assigned for patients who had no comorbidities with COPD. The second group was dedicated for patients suffering from one comorbidity and the third group included patients with more than one comorbidity.

Pulmonary rehabilitation

All patients underwent PR program with optimization of pharmacological therapy and/or long term oxygen therapy according to standard guidelines. Exercise training targeted upper and lower extremity muscles. For lower extremity, aerobic exercise on treadmill was done. The applied method of training was interval training; 3 min of exercise alternating with 3 min of rest and intensity of training was targeted to reach 60–80% of maximal heart rate but was modified according to patient's tolerance. Upper extremity exercise was in the form of repetitive lifting of free weights. Thirty repetitions were performed of weights that were determined according to patient's tolerance. Increased weights were used by the start of each new week. The training program ran for 8 weeks, 3 sessions per week under supervision. In addition, patients' education wad done, including instructions for disease self-management (prevention and early treatment of exacerbations, breathing strategies and bronchial hygiene techniques) [6].

Outcome measurement

The following physiological/functional parameters were recorded for all patients at the baseline and at the end of the program. Airway obstruction was measured by post-bronchodilator spirometry.

Functional exercise capacity was assessed using the six-minute walk distance (6MWD) performed according to American Thoracic Society guidelines [12]. Dyspnea was assessed by the modified Medical Research Council (mMRC) scale [13]. Quality of life was gauged via St. George's Respiratory Questionnaire (SGRQ) [14]. Aerobic capacity was estimated by calculating maximum oxygen consumption (VO_{2max}) via the modified Rockport walking test (RWT) [15]. The formula used to calculate the VO_{2max} was:

$$132.853 - (0.0769 \times \text{Weight}) - (0.3877 \times \text{Age}) + (6.315 \times \text{Gender}) - (3.2649 \times \text{Time}) - (0.1565 \times \text{Heart rate})$$

where weight is in pounds; gender is coded as Male = 1 and Female = 0; time is expressed in minutes and 100th of a minute and it refers to time taken to complete 400 m or till reaching degree of fatigue; maximum heart rate is in beats/minute and age is in years.

The concept of the minimal clinically important difference (MCID) to determine response to PR was used [16]. Improvements were determined by the following cut-off points: exercise capacity [+30 m in the 6MWD], [17] dyspnea [−1 point on the mMRC dyspnea scale] [18] and health status [−4 points on the SGRQ] [19]. For FEV_1%, the MCID was set as change by 7.5% [20]. We calculated the MCID for aerobic capacity (VO_{2max}) using the distribution method, which determines the MCID for a specific test as 0.5 standard deviation (SD) of the variable in the studied population [20]. One SD for VO_{2max} was 19 ml/kg/min and thus the MCID following PR was decided as increase by 9.5 ml/kg/min.

Statistical analysis

All statistical analyses were performed using PASW software (version 17; SPSS Inc., Chicago, IL, USA). All results were considered statistically significant at $p < 0.05$. Quantitative variables were presented as mean ± SD. Means for parametric variables were compared by student T-test or ANOVA according to situation. Non parametric quantitative variables were compared by Mann–Whitney test and Kruskal–Wallis test according to situation. Qualitative variables were presented as frequencies and comparisons were made by Chi square test.

A comparison was made between the three comorbidity groups according to baseline demographic, clinical and physiologic parameters. The comparison of physiologic parameters was repeated after concluding the PR program. The group of responders was then compared with the non-responders and variables that showed significant difference were entered into logistic regression.

Results

This study recruited 55 patients to undergo PR. Fifteen patients did not complete the program either due to lack of perceived benefit or problems with transportation. Data of patients who dropped out were not included. Thirty-four patients (85%) had comorbidities. Fig. 1 demonstrates the frequencies of the recorded comorbidities. Cardiovascular disease included systemic hypertension, cor pulmonale, cerebro-vascular stroke and valvular heart disease. Metabolic disorders comprised diabetes mellitus and dyslipidemia. Accordingly patients were divided into three groups based on comorbidities as shown in Fig. 2. A comparison between the comorbidity groups according to baseline characteristics is shown in Table 1. Patients with one comorbidity were significantly younger than patients without comorbidities (data not shown). Bone mineral density (BMD) was significantly lower among patients with comorbidities. Most patients (36) belonged to stage D according to the new GOLD classification. Except for FEV_1%, all other functional parameters were significantly different between groups (Table 1) and consistently worse for patients with more than one comorbidity (data not shown). After completion of the PR program, the comparison between groups according to functional parameters was repeated (Table 2). Again except for FEV_1%, the mean values for functional parameters have improved in all comorbidity groups, but the inter-group differences have become statistically insignificant (Table 2). By applying the MCID for mMRC, 6MWD, SRGQ and VO_{2max} the number of patients who achieved these preset values was 32 (80%). Table 3 demonstrates a comparison between responders (32) and non-responders (8) according to baseline characteristics as well as the frequency of different comorbidities. Responders had significantly higher values of $PaCO_2$, baseline mMRC score and SGRQ score and lower values of baseline 6MWD and VO_{2max} (Table 3). When these variables were entered into regression model to predict response to PR, none of them stood the test of significance, likely due to the relatively small sample size.

Discussion

The present study strove to observe the prevalence of comorbidities in patients with COPD and to evaluate whether baseline physiological and functional characteristics as well as specific comorbidities may predict a poorer response to PR.

Diagnosis of COPD was done according to the more-inclusive new staging system proposed by GOLD [3] that depends not only on the severity of airflow limitation but also on the degree of dyspnea and the frequency of occurrence of exacerbations. Previous studies in the same subject relied

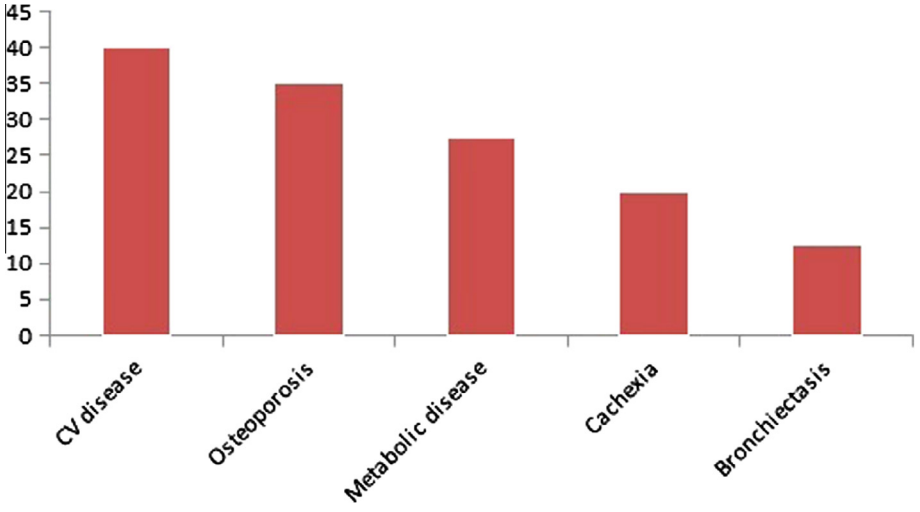

Figure 1 Bar chart comparing frequencies of different comorbidities among studied patients.

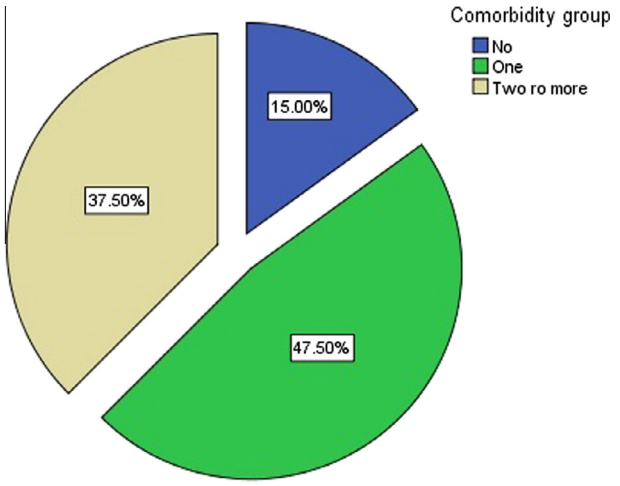

Figure 2 Pie chart demonstrating sizes of the three study groups.

mainly on the old GOLD classification that took into consideration the degree of air obstruction only [8–10,21]. The majority of our patients (90%) belonged to group D underscoring the fact that this cohort of patients was symptomatic and frequently experienced exacerbations.

Comorbidities were highly prevalent in the studied cohort and occurred in 34 patients (85%). Similarly high proportions were reported in previous studies, ranging between 50% and 98.5% [8–10,21]. In one of the largest studies addressing the topic of comorbidities and COPD, Divo et al. [22] reported that in their cohort of 1664 patients, the average number of comorbidities was 6 + 3.5 per subject for the whole cohort.

It is no wonder that patients with severer forms of COPD commonly report comorbidities as both the severity of the diseases and the systemic manifestations/comorbidities have causal link to systemic inflammation [5].

The most prevalent comorbidities in our cohort (cardiovascular disease in 40% of patients and osteoporosis in 35%) have been linked to systemic inflammation in COPD patients. Systemic inflammation observed in COPD is chiefly responsible for pulmonary and systemic endothelial dysfunction [23]. Also this intense inflammation in addition to hypoxia and protease/antiprotease imbalance have all been found to be contributory to the development of osteoporosis in the advanced stages of COPD [24].

The cohort of patients with comorbidities tended to be younger than COPD patients without any comorbidity (Table 1). There was no statistically significant difference in the smoking index between comorbidity groups to account for this age difference. Whether the presence of comorbidities predisposes patients with COPD to be symptomatic at an earlier age is a question that needs further investigation in future research.

In the studied patients, the presence of comorbidities significantly affected the values of 6MWD, mMRC and SGRQ, and VO_{2max}. Patients without comorbidities, when compared to the other two groups, tended to have less dyspnea, better quality of life and more exercise tolerance.

The worsened functional and symptomatic status of patients with COPD and comorbidities has been observed in

Table 1 Anthropometric, demographic and functional characteristics among comorbidity groups at baseline. Data are presented as mean ± SD for continuous variables and frequencies for categorical variables.

	All patients	Comorbidity groups			*p*-value
		0	1	>1	
Age years	60.38 ± 8.9	68.17 ± 8.1	57.79 ± 8.5	60.53 ± 8.4	**0.041**[*]
Males/females *n*	37/3	6/0	17/2	14/1	0.686[†]
PYI pack years	59.34 ± 27.9	37.5 ± 11.3	65.37 ± 33.7	61.7 ± 21.12	0.069[‡]
BMI kg m^{-2}	24.24 ± 5	24.78 ± 3.9	23.22 ± 4.08	25.3 ± 6.4	0.483[*]
LTOT *n*	10 (25%)	0	5	5	0.276[†]
pH	7.41 + 0.06	7.43 ± 0.02	7.42 ± 0.04	7.40 ± 0.09	0.707[*]
$PaCO_2$ mmHg	40.8 ± 8.1	39 ± 2.5	40.16 ± 10	42.47 ± 6.8	0.635[*]
PaO_2 mmHg	72.4 ± 14	82.3 ± 17	72.53 ± 11.8	68.4 ± 14.23	0.173[*]
BMD SD	−2.13 ± 0.64	−1.35 ± 0.69	−2.16 ± 0.54	−2.45 ± 0.46	**0.001**[*]
GOLD *n*					0.600[†]
B	2	0	1	1	
C	2	0	2	0	
D	36	6	16	14	
FEV_1%	32.1 ± 11	35.9 ± 7	32.24 ± 11	30.42 ± 11.9	0.600[*]
mMRC	2.78 ± 0.83	2 ± 0.63	2.56 ± 0.89	3.22 ± 0.54	**0.007**[‡]
6MWD meters	183 ± 83.5	253 ± 85.7	192 ± 84.5	143.6 ± 61	**0.040**[‡]
SGRQ %	71 ± 15.5	57.21 ± 18.9	69.76 ± 16.4	78.15 ± 7.88	**0.014**[*]
VO_{2max} ml/kg/min	39.5 ± 19	52.3 ± 7.5	41.28 ± 19.8	30.23 ± 18.9	**0.045**[‡]

SD, standard deviation; PYI, pack year index; BMI, body mass index; LTOT, long term oxygen therapy; BMD, bone mineral density; GOLD, global strategy for chronic obstructive pulmonary disease; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; FEV_1, forced expiratory volume in one second; mMRC, modified Medical Research Council dyspnea scale; 6MWD, six minute walk distance; SGRQ, Saint George Respiratory Questionnaire; VO_{2max}, maximum oxygen consumption.
Bold = significant at *p* value < 0.05.
[*] ANOVA.
[†] Chi-square.
[‡] Kruskal–Wallis.

Table 2 Outcome measures at the end of program among comorbidity groups. Data are presented as mean ± SD.

	All patients	Comorbidity groups			*p*-value
		0	1	>1	
FEV_1%	31.8 ± 10.1	36 ± 8	31.38 ± 10.4	30.75 ± 10.8	0.556*
mMRC	1.33 ± 0.8	0.83 ± 0.98	1.21 ± 0.97	1.67 ± 0.61	0.111†
6MWD meters	338.7 ± 106	371.7 ± 144	364.7 ± 102	292.7 ± 82	0.101†
SGRQ %	48 ± 14.3	41.9 ± 17	46.5 ± 16.3	52.4 ± 9.4	0.266*
VO_{2max} ml/kg/min	60 ± 11.9	61.1 ± 13.8	64 ± 9.57	54.48 ± 11.9	0.068†

SD, standard deviation; FEV_1, forced expiratory volume in one second; mMRC, modified Medical Research Council dyspnea scale; 6MWD, six minute walk distance; SGRQ, Saint George Respiratory Questionnaire; VO_{2max}, maximum oxygen consumption.
* ANOVA.
† Kruskal–Wallis.

Table 3 Comparison between responders and non-responders to pulmonary rehabilitation according to baseline anthropometric, physiologic, clinical and functional parameters. Data are presented as mean ± SD for continuous variables and frequencies for categorical variables.

	Responders (n = 32)	Non-responders (n = 8)	*p*-value
Age years	59.2 ± 8.69	65 ± 8.86	0.127*
Sex male/female	29/3	8/0	0.368‡
PYI pack years	60.67 ± 28.85	54.38 ± 25.27	0.665†
GOLD B/C/D	1/1/30	1/1/6	0.287‡
LTOT n	9	1	0.361‡
pH	7.42 ± 0.04	7.39 ± 0.12	0.482*
PCO_2 mmHg	41.8 ± 8.61	37 ± 3.92	**0.028***
PO_2 mmHg	70.5 ± 13.31	80.3 ± 15.46	0.133*
BMD SD	−2.26 ± 0.55	−1.58 ± 0.75	0.058*
BMI kg m^{-2}	23.8 ± 5.12	25.9 ± 4.71	0.300*
Cachexia	8	0	0.114‡
CV disease	12	4	0.519‡
Osteoporosis	14	0	**0.020**‡
Metabolic disease	8	3	0.479‡
Bronchiectasis	5	1	0.232‡
Baseline FEV_1%	30.9 ± 10.77	36.8 ± 11.47	0.215*
Baseline 6MWD m	167.5 ± 81.59	246.1 ± 61.27	**0.012**†
Baseline VO_{2max} ml/min	35.82 ± 19.38	54.51 ± 6.33	**0.007**†
Baseline mMRC	2.94 ± 0.75	2.13 ± 0.83	**0.019**†
Baseline SGRQ	72.86 ± 14.40	63.66 ± 18.82	0.228*
0 Comorbidity	3	3	0.068‡
1 Comorbidity	12	3	0.872‡
>1 Comorbidity	17	2	0.204‡

SD, standard deviation; PYI, pack year index; GOLD, global strategy for chronic obstructive pulmonary disease; BMI, body mass index; LTOT, long term oxygen therapy; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; BMD, bone mineral density; FEV_1, forced expiratory volume in one second; mMRC, modified Medical Research Council dyspnea scale; 6MWD, six minute walk distance; SGRQ, Saint George Respiratory Questionnaire; VO_{2max}, maximum oxygen consumption.
Bold = significant at p value < 0.05.
* Independent T test.
† Mann–Whitney test.
‡ Chi-square test.

previous studies. Even after accounting for differences in age, sex and smoking history, COPD patients with comorbidities, in particular cardiovascular disease and DM, were found to be generally more dyspneic and had a reduced exercise capacity in comparison to patients without comorbidities [25]. The presence of three or more comorbid diseases in COPD was found to be more predictive of decreased health status than any demographic or clinical variable [26].

The presence of these comorbid conditions worsens the feeling of dyspnea on exertion which predisposes patients to lead a sedentary life. Deconditioning is thus, at least, partially responsible for the poorer functional status of patients with comorbidities. Skeletal myopathy and metabolic abnormalities noted in chronic diseases that are much similar to changes noted in COPD are also responsible for such poor status [27].

The PR program was offered to patients during convalescence from acute exacerbation. This choice was based on a systematic review conducted by Puhan and colleagues of clinical trials studying PR in COPD patients following acute exacerbations [28]. It demonstrated a significant reduction in the odds of hospital admission, in addition to large consistent improvements in the SGRQ total score, and the domain scores for activity limitation and impact [28].

Examining the values of measurements of assessments at the end of program for the three comorbidity groups, the previously noted inter-group wide differences in 6MWD, VO_{2max}, mMRC and SQRG have narrowed after PR. These findings might serve to prove that the severer impairment noted in COPD patients who have comorbidities in comparison to patients without comorbidities is modifiable rather than permanent. Breaking the vicious circle of deconditioning that causes exercise limitation uncovered a considerably better potential to perform effort than what was apparent initially.

Determining response to PR in each patient relied on the concept of MCID which provides a guide as to whether an intervention provides a minimum level of perceived benefit and transcends the concept of statistical differences [20].

The overall improvement after PR was noted in 80% of patients, which is in accordance with the findings of previous studies who reported response rates of >50% [6].

Drawing a comparison between responders and non-responders, there were significant differences in baseline $PaCO_2$, 6MWD, VO_{2max}, mMRC and frequency of osteoporosis where responders always had the worse levels. Crisafulli et al. [8] found that higher values of $PaCO_2$ were associated with better outcome after PR. The same researchers also concluded that the worse the baseline condition (lower 6MWD or higher mMRC) was, the more likely it was that the patient

responded well to PR. They argued that a degree of improvement less than the MCID in patients with a better baseline condition could be due to a "ceiling effect" [8]. These findings inform us that inclusion of patients with poorer physical performance and lower gas exchange capacity corresponds to a more elevated probability of improving their functional status.

It is certainly noteworthy that this study did not find that the presence of one or more comorbidities had negative effect on the response to PR. Earlier research [9] has provided a completely different view, where the impact of comorbidities was reported to inversely predict the improvement of both exercise tolerance and QoL after PR. More recent research (by the same investigator) found results similar to the present study and concluded that individual comorbidities (either alone or in combination) did not preclude indication and/or effectiveness of a PR course [8].

Study limitation

The formula of modified RWT to estimate VO_{2max} was used. The present study has found this formula to be inaccurate in estimating the values of VO_{2max}, mostly over-estimating the results (when compared to expected values according to age). It was used, nonetheless, as a rough guide to the changes that occurred in each patient. Cardiopulmonary exercise testing would be recommended as a much more accurate tool. The small number of non-responders to PR imposed considerable hindrance to performing regression analysis to find the variables that could predict a negative response to PR. This limitation might have been solved with a larger patient sample.

Conclusions

Comorbidities commonly associate COPD and they worsen the functional and physiologic impairments seen in these patients. Patients with comorbidities demonstrate better response to exercise training in the context of PR when compared with patients without comorbidities and thus the presence of comorbidities should encourage the inclusion of patients with COPD to PR. Future research will need to verify the factors that can predict poor response to PR. Another question that deserves answering is whether PR by itself can have effect, either positive or negative, on comorbidities in patients with COPD.

Conflict of interest

None to be declared.

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